COMPLICATIONS OF FALCIPARUM MALARIA*

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I PROPOSE to talk on the genesis and treatment of coma in malaria. The usual explanation given by pathologists for cerebral damage in falciparum malaria is the sometimes demonstrable "blocking" of the small vessels by parasitized erythrocytes. I am sure this is *post hoc* rather than *propter hoc* and is, in a sense, an artifact. It represents a late and usually irreversible development.

In my opinion the primary cause of coma is physiological barrier of the cerebral circulation. This is brought about by alteration of the function of the endothelial cells which are normally highly impermeable but which become permeable to protein (especially albumin) and so allow leakage of water. The protein and water leak into the contiguous brain tissue, where they cause some local edema, and into the cerebrospinal space through the blood-brain barrier. Since the villi are similarly disturbed, the protein passes freely back into the blood stream, so that the cerebrospinal fluid protein content becomes only moderately raised. This is quite different from the state of affairs in inflammatory meningitis, where protein can be shown to leak from the inflamed meningitic vessels but is *not* returned through the undisturbed villi; hence the cerebrospinal fluid protein content readily mounts.

The leakage of protein and of the accompanying water causes local increase in plasma viscosity and eventually stasis with packing of erythrocytes into a homogeneous mass which is essentially similar to that which occurs in vessels in acute inflammation.

The local circulation then slows and may come to a stop. I think it is this effect which finally induces coma in the patient.

The stasis is reversible for some time but eventually becomes irreversible, at which stage I suspect the balance of coagulation and fi-

*Presented as part of a *Symposium on Malaria* sponsored by The Tropical Disease Center, St. Clare's Hospital, New York, N.Y. and The Merck Company Foundation, Rahway, N.J., held at the Center, May 17, 1969.

brinolysis is tipped to the side of some intravascular clotting (which is seldom extensive and often not seen at all); this may be aggravated by "sludging."

This physiological picture occurs in many acute medical conditions, but in malaria it is complicated by the presence of the parasite and the specific effects it has on the host cell. The so-called plugging comes about because of the bursting of mature schizonts somewhere in the packed stased erythrocytes and high local infection rate caused by the merozoites.

If coma is due to the failing of the cerebral circulation, restoration of flow should be followed by recovery from coma. This is what I think happens immediately, but in the patient with malaria the ultimate outcome depends on two other factors: 1) the degree of irreversible damage which has occurred before therapy, and 2) the removal of the malaria parasites from the blood.

Thus in two comatose patients with severe falciparum malaria immediate treatment may restore consciousness in a few hours, but one patient may survive because the cerebral damage is largely reversible. This is independent of the rapid clearance of parasites in both cases.

Before I touch on the treatment of coma in malaria, let me summarize the experimental evidence for what I have said. We have demonstrated movement of albumin and water from cerebral vessels with the cerebral substance and the cerebrospinal fluid in both *Plasmodium berghei* and *Plasmodium knowlesi* infection, with the use of fluorescent, radioactive, and chemical and histochemical methods. We have demonstrated the edema by measuring dessicated brain weights and comparing the nitrogen and water content of samples of brain tissue. There is no doubt that the movement of protein and water occurs during the periods of high parasitemia.

We have also evidence of many factors in the circulation or at the tissue face which affect endothelial permeability in this way. Kininogens fall, kininogenases increase, kinin levels remain within normal limits despite a sometimes 10-fold increase in kininases; histamine and adenosine plasma levels rise. And so on—most of this has already been published, including the evidence of the existence of a toxic factor which inhibits oxidative phosphorylation in cell mitochondria, including those of endothelium.

Major support for the idea, however, comes also from treatment

in the experimental model (and, as I see it, in falciparum malaria) once the escape of protein and water is stopped with extreme rapidity by cortisone and *by quinine and chloroquine.* All these compounds have very active anti-inflammatory actions, and here they act on the inflammatory stasis.

What is needed in the human case is an anti-inflammatory drug. We are lucky to have quinine and chloroquine which not only fulfill this requirement but are also antiparasitic.

In giving these drugs for cerebral malaria (let us say, for falciparum malaria) we are benefiting first by their anti-inflammatory activity and later by their antiparasitic action. In coma it is the former that counts, not the latter. This is obvious enough on the timing; recovery from coma after intravenous quinine occurs long before the drug has had time to act decisively on the parasite.

In most comatose cases that I have treated, I have found these drugs enough. I have not often felt justified in adding cortisone compounds, and I am not convinced that they are needed as a routine, as some advise.

Now a word about the pathogenesis and treatment of liver damage in infection from *Plasmodium falciparum.* All infections are associated with much evidence of liver damage, sometimes severe. The primary processes which initiate the hepatic disturbance are also sometimes associated with the onset of medical shock, sometimes not, but there is always considerable hyperactivity of the sympathetic nervous system. This is very clearly established in *P. knowlesi* malaria in macaque monkeys.

One effect of this is the constriction of visceral vessels and the resultant restriction of organ blood flows in the liver (and in the kidney). In the liver the small branches of the portal vein are most involved and the result of this constriction is portal venous hypertension and degeneration and necrosis of parenchymal cells in the centrilobular zones of the lobules, where the restricted blood flow and the inhibition of oxidative phosphorylation are additive.

We have found it possible in *P. knowlesi* malaria to release the portal venous constriction by adrenergic blockade. Ray produced a similar effect by sympathectomy before infection.

I suggest that in early hepatic failure in falciparum malaria it might be worth trying adrenergic blockade (for example by dibenzylene)

which would not only relieve the circulating disturbances in the liver, but also in the vasconstricted kidney, in which acute anuric failure is not uncommon. (It is important to distinguish between the physiological circulating renal failure, which we demonstrated 25 years ago in blackwater fever, and the chronic renal lesions which appear in *Plasmodium* malariae infections, which probably have an immunological basis.)

I suppose what I am trying to say is: remember your physiology.